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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/992,680	11/19/2001	Chi-Huey Wong	84503	1046

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EXAMINER

PRATS, FRANCISCO CHANDLER

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 05/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/992,680

Applicant(s)

WONG ET AL.

Examiner

Francisco C. Prats

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 February 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-26, 28, 29 and 52-57 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-26, 28, 29 and 52-57 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 11-29-02.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 14, 2005, has been entered.

The amendment filed February 14, 2005, has been received and entered. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claims 21-26, 28, 29 and 52-57 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-26, 28, 29 and 52-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

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particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the new language requiring the enzymes to be "utilized in a single reaction mixture" renders the claims indefinite. First, it is unclear how a limitation directed to a prospective method of using the claimed compositions can properly limit the present claims. That is, all of the claims under examination are directed to compositions. It is unclear how claim language proposing to limit the methods whereby the compositions are to be used can possibly limit the claims. For example, a claim reciting "a composition comprising aspirin, utilized in the treatment of headache" would simply read on a composition comprising aspirin. The "utilized" limitation does not change the aspirin composition in any way. It is therefore confusing how the new "utilized" step limits the claims, if at all.

Second, the recitation "utilize" is equivalent to the term "use." Because the claims fail to state the actual positive steps by which the enzymes are utilized, it is unclear what the claims encompass.

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 21 is rejected under 35 U.S.C. 102(b) as being anticipated by Liepkans et al (Eur. J. Biochem. 168:209-217 (1987)) or Muramatsu et al (Eur. J. Biochem. 157 :71-75 (1986)).

Claim 21 reads on a cell or cell homogenate contained within a vessel. Each of the cited references discloses a vessel-contained cell or cell homogenate capable of transferring fucosyl moieties to acceptor moieties. See, e.g., Liepkans at page 210, disclosing cell pellets; see Muramatsu at page 72, Table 1, disclosing cell homogenate with fucosyltransferase activity. The donor fucosyl moieties are disclosed as being GDP-fucose. For the cells to make the GDP-fucose required for fucosyltransferase activity, the cells inherently possessed an enzyme capable of generating GDP-fucose. Thus, the cells/cell homogenates of Liepkans and Muramatsu necessarily contained both enzymes required in the claims, in an *in vitro* system. A holding of anticipation is therefore clearly required. Note

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that this rejection could be overcome by requiring the enzymes recited in the claims to be "isolated."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-23, 25, 52, 54 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergh et al (U.S. Pat. 4,925,796) in view of Prieels et al (J. Biol. Chem. 256(20):10456-10463 (1981)) and Schachter et al (Methods Enzymol. 28:285-287 (1972)).

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Bergh discloses compositions comprising a fucosyltransferase and GDP-fucose, for use in fucosylation of oligosaccharide moieties of glycoproteins. See column 18, lines 33-68; see also claim 25 at column 26. Bergh explicitly discloses that suitable fucosyltransferases are those disclosed by Prieels. See column 18, 55-58. Bergh differs from the cited claims in failing to include the claimed GDP-fucose forming enzymes, fucose kinase and GDP-pyrophosphorylase, in his composition. However, Schachter clearly discloses that the GDP-fucose required in the fucosylation process of Bergh can be prepared using the very enzymes recited in the claims. Note the presence of both GDP and GTP in the reaction milieu of Schachter, as evidenced by the reaction equilibrium equation on page 285.

Thus, solely looking to the cited prior art, the artisan of ordinary skill would have been motivated to have combined the enzymes and substrates of Schachter with the fucosyltransferase of Bergh so as to generate the GDP-fucose required for Bergh's fucosylation process. Particular motivation for combining the fucosyltransferase of Prieels, as suggested by Bergh, with the GDP-fucose-synthesizing enzymes of Schachter, would have been derived from the disclosure by Prieels that the fucosyltransferases disclosed therein have a fairly wide pH

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optimum ranging from pH 6.5 to pH 8.5 (Prieels, e.g., Fig. 7, at page 10461), which encompasses the very pH used by Schachter, pH 8 (Schachter, page 285), to prepare GDP-fucose. Thus, the artisan of ordinary skill, recognizing that Bergh's oligosaccharide-synthesizing process requires GDP-fucose as a starting material, and further recognizing from Schachter that the GDP-fucose starting material can be made enzymatically at a pH directly compatible with Bergh's fucosyltransferases (as evidenced by Prieels), clearly would have been motivated to have combined the enzymes responsible for production of the GDP-fucose starting material with the enzyme responsible for producing the oligosaccharide, with a reasonable expectation that the resulting combination of enzymes would result in the production of the oligosaccharide compounds disclosed by Bergh as being desirable. A holding of obviousness is therefore required.

Claims 21-25, 52, and 54, 55 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergh et al (U.S. Pat. 4,925,796) in view of Prieels et al (J. Biol. Chem. 256(20):10456-10463 (1981)) and Schachter et al (Methods Enzymol. 28:285-287 (1972)), as applied to claims 21-23, 25, 52,

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54 and 56 above, and in further view of Demain et al (U.S. Pat. 4,178,210).

As discussed above, when taken in light of Schachter, Bergh renders obvious the compositions recited in claims 21-23, 25, 52, 54 and 56. Neither Bergh nor Schachter discloses the presence of pyruvate kinase in their compositions as recited in claim 24. However, in view of the fact that Schachter's process requires ATP, the artisan of ordinary skill would have considered the use of the well-known PEP/pyruvate kinase ATP regeneration system an obvious method of regenerating the ATP required for the ultimate synthesis of the GDP-fucose required in Bergh's fucosylation process. See, e.g., Demain at column 4, lines 23-26 ("[t]he preferred phosphate donor is phosphoenolpyruvate and its corresponding phosphotransferase enzyme, pyruvate kinase.") Thus, the claimed use of pyruvate kinase in an enzymatic system known to require ATP must be considered obvious.

Claims 21-26, 28, 29 and 52-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergh et al (U.S. Pat. 4,925,796) in view of Prieels et al (J. Biol. Chem. 256(20):10456-10463 (1981)) and Schachter et al (Methods Enzymol. 28:285-287 (1972)) and Demain et al (U.S. Pat.

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4,178,210), as applied to claims 21-25, 52, and 54, 55 and 57, above, and in further view of Yamamoto et al (Agric. Biol. Chem. 48(3):823-824 (1984)).

As discussed above, when taken in light of Schachter and Demain, Bergh renders obvious the process recited in claims 21-25, 52, and 54, 55 and 57. None of Schachter, Demain or Bergh discloses the presence of an NADPH regenerating system as recited in claim 26, or the *in situ* generation of GDP mannose via the components recited in claims 28, 29 and 56. However, Yamamoto clearly discloses that compositions comprising the claimed ingredients, including the NADPH regenerating system (right column, page 283, lines 18-21), result in the production of GDP-fucose from GDP-mannose. Moreover, Yamamoto discloses that the GDP-fucose so synthesized is suitable for use as a fucosyltransferase substrate. See first sentence page 285. Thus, the artisan of ordinary skill, recognizing that the GDP-fucose required in Bergh's process was suitably prepared using either Yamamoto's or Bergh's system, would have been motivated to have included the enzymes required for said syntheses in Bergh's fucosylation compositions. Moreover, the inclusion of a pyruvate kinase/PEP system in such a composition would have been obvious in view of the requirement for GTP in the synthesis of the GDP-mannose used by Yamamoto's system.

In sum, the claims recite an assembly of the enzymes known in the prior art to be useful in the synthesis of fucosylated oligosaccharides. The artisan of ordinary skill, recognizing solely from the prior art that the claimed combinations of enzymes were suitable in the preparation of fucosylated oligosaccharides, clearly would have been motivated to have assembled the claimed ingredients into a single composition. Absent some demonstration of an unexpected result coming from the claimed combination, a holding of obviousness is clearly required.

Response to Arguments

All of applicant's argument submitted to date has been fully considered, and reconsidered, but is not persuasive of error.

Applicant urges that because Schachter separated the fucose kinase and GDP-fucose pyrophosphorylase enzymes in his two-step GDP-fucose synthesis, Schachter demonstrates that the prior art recognized that it was necessary to separate the two enzymes, and that therefore Schachter teaches away from the claimed invention, wherein the fucose kinase and GDP-fucose pyrophosphorylase enzymes are present in the a single composition. Applicant urges that this is necessarily true

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because the extra work would not have been performed had it not been needed.

Note that this argument is only relevant to claim 25, the only claim requiring a fucose kinase. With respect to claim 25's requirement of a fucose kinase and GDP-fucose-forming enzyme together in a single reaction vessel, contrary to applicant's argument, Schachter discloses that the two enzymes both function at pH 8.0. Compare, reaction media disclosed on pages 285 and 286 of Schachter. Thus, one of ordinary skill clearly would have recognized that, because the enzymes are disclosed as being functional at the same pH and in reaction media having the same cofactors and buffer present, the enzymes would have functioned together in a single reaction vessel. Applicant's assertion, to the effect that the enzymes would have been allowed to act together had they been so capable, is mere speculation and not based on any fact currently of record. We do not know why Schachter separated the enzymes. However, by purifying the enzymes they are rendered more concentrated (i.e. are present as a greater percentage of the reaction medium), and are therefore more efficient in synthetic processes, as is common in enzymatic synthetic processes. This does not mean the enzymes will not work together. The enzymes may have been separated to characterize the individual product yields after

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each step. The only true fact is that it is not clear why the steps were performed separately. Thus, it is simply improper to conclude that the enzymes were necessarily incapable of functioning together, merely because they were used separately. There is no fact of record to support this assertion.

Applicant urges that the Capasso, Paulson and Larsen references (Exhibits 1-3) establish that fucosyltransferase enzymes are specific to the golgi apparatus. Applicant urges that Cosson et al (Exhibit 4) and Exhibit 5 (<http://mcb.berkeley.edu/courses/mcbl37/exercises/Lessong%zo%zopH%zoRegulation.pdf>) demonstrate that the golgi has a different pH than the cytosol. Thus, applicant urges that because fucosyltransferases are from the golgi, and because the environments in the golgi and the cytosol are different with respect to pH, one of ordinary skill would not expect to be able to combine golgi enzymes with cytosol enzymes in a multi-enzyme synthesis, as asserted in the pending obviousness rejections.

However, Prieels clearly demonstrates the purification of at least two fucosyltransferase activities from human milk. See, e.g., abstract. Moreover, as discussed above, Prieels discloses that the purified fucosyltransferases have a fairly wide pH optimum ranging from pH 6.5 to pH 8.5 (Prieels, e.g., Fig. 7, at page 10461), which encompasses the very pH used by

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Schachter, pH 8 (Schachter, page 285), to prepare GDP-fucose. Thus, while fucosyltransferases are present in the golgi as argued by applicant, and the golgi does in fact have a different pH, Prieels demonstrates that fucosyltransferases may also be isolated from sources other than the golgi. Prieels also demonstrates that fucosyltransferase have properties which would motivate the artisan of ordinary skill to use them in combination with the enzymes disclosed by Schachter as producing the GDP-fucose donor moiety required by the fucosyltransferases. In sum, the artisan of ordinary skill would have recognized from Schachter that the starting materials required for the Prieels/Bergh fucosyltransferase process would have been prepared using Schachter's enzymes at a pH directly compatible with Bergh's fucosyltransferases (as evidenced by Prieels). The artisan of ordinary would therefore have been motivated to have combined the enzymes responsible for production of the GDP-fucose starting material with the enzyme responsible for producing the oligosaccharide, so as to prepare the starting material for Bergh's synthesis, *in situ*.

Applicant further argues that Exhibits 6 and 7 demonstrate the recognition in the art of feedback inhibition with respect to fucosyltransferase enzymes, and that this supports the assertion that one of ordinary skill would have expected adverse

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interactions resulting from the combination of enzymes in a multi-enzyme system. However, if the well known effects of product inhibition were considered a deterrent to the motivation for performing enzymatic syntheses, then the artisan of ordinary skill would not have been motivated to have performed any enzymatic synthesis, since all enzymatic processes are subject to product inhibition. In view of the ubiquity of enzymatic processes in the prior art, applicant's argument fails from a logical standpoint, since if there were no motivation to perform enzymatic assays, no one would perform them.

Applicant's assertion that Schachter does not use a catalytic amount of enzyme is simply incorrect. The reference demonstrates that the enzymes catalyze the reaction. It is unclear why applicant continues to argue this point.

As to the alleged use of hindsight with respect to the Yamamoto reference, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Moreover, it is respectfully pointed

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out that combining two enzymes, as recited in the claims at their broadest herein, requires little in the manner of hindsight,

Lastly, as to the alleged alleviation of a long felt need, applicant's argument fails to point out, and it is not clear from the reference, which of claimed embodiments is responsible for alleviating the long felt need, and whether there is truly a nexus between what is recited in the claims, and the alleviation of that need. On the current record, it does not appear that combining two enzymes resulted in the savings urged by applicant. Rather, it appears that a multi-enzyme synthetic process, not claimed herein, producing a sialylated product not recited in the claims herein, was used in the synthetic processes described in the Borman reference.

In sum, because the prior art suggests practicing the invention as claimed, the holding of obviousness remains required.

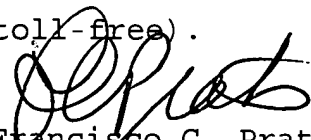
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C. Prats whose telephone number is 571-272-0921. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Francisco C. Prats
Primary Examiner
Art Unit 1651

FCP